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FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 15:42:55 ON 18 JUL 2000

L1 817 S ELASTIN(W)GENE
L2 14 S MOUSE(3A)L1
L3 9 DUP REM L2 (5 DUPLICATES REMOVED)
L4 3 S (MOUSE OR MICE)(W)ELASTIN(3A)(GENE OR DNA OR NUCLEOTIDE(W)SEQ
L5 3 DUP REM L4 (0 DUPLICATES REMOVED)
L6 4 S (MOUSE OR MICE)(W)TROPOELASTIN(3A)(GENE OR DNA OR NUCLEOTIDE(
L7 1 DUP REM L6 (3 DUPLICATES REMOVED)

=> d bib ab 1-4 15

L5 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2000 ACS
AN 1996:372832 CAPLUS
DN 125:111259
TI Elastin gene mutations in transgenic mice
AU Sechler, Jan L.; Sandberg, Lawrence B.; Roos, Philip J.; Snyder, Ida; Amenta, Peter S.; Riley, David J.; Boyd, Charles D.
CS Johnson Medical School, UMDNJ-Robert Wood, New Brunswick, NJ, 08903, USA
SO Ciba Found. Symp. (1995), 192(Molecular Biology and Pathology of Elastic Tissues), 148-171
CODEN: CIBSB4; ISSN: 0300-5208
DT Journal; General Review
LA English
AB A review, with 39 refs., of work done in the authors lab. using several rat tropoelastin minigene recombinants encoding the complete sequence of rat tropoelastin, two isoforms of rat tropoelastin and a truncated tropoelastin lacking the domains encoded by exons 19-31 of the rat gene. Coding and non-coding domains in all these recombinants were placed under the transcriptional control of 3 kb of the promoter domain of the rat tropoelastin gene. These minigenes were used to prep. a total of 28 sep. founder lines of transgenic mice. A species-specific reverse-transcriptase polymerase chain reaction (RT-PCR) assay was established to demonstrate the synthesis of rat and mouse tropoelastin mRNA in several tissues obtained from both neonatal and adult transgenic mice. Thermolytic digestion of insol. elastin isolated from several neonatal mouse tissues revealed the presence of rat tropoelastin peptides in progeny from all those founder mice in which detectable levels of rat tropoelastin mRNA were noted. Phenotypic and histopathol. assessment of transgenic and non-transgenic animals revealed the development of two diverse elastic tissue disorders. The progeny of two sep. founder lines overexpressing the rat tropoelastin isoform lacking exon 33, developed an emphysematous phenotype in early adulthood. In contrast, transgenic mice, in which expression of the truncated rat tropoelastin minigene lacking exons 19-31 had been obsd., died of a ruptured ascending aortic aneurysm. Tropoelastin gene mutations, therefore, will result in heritable disorders of elastic tissue. Moreover, different mutations in the tropoelastin gene

will be responsible for very different abnormalities in elastic tissue function.

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2000 ACS
AN 1995:668015 CAPLUS
DN 123:48857
TI Elastin gene mutations in transgenic mice
AU Sechler, Jan Louise
CS Rutgers the State U. of N.J. and U.M.D.N.J., New Brunswick, NJ, USA
SO (1994) 204 pp. Avail.: Univ. Microfilms Int., Order No. DA9511991 From: Diss. Abstr. Int. B 1995, 55(12) 5209
DT Dissertation
LA English
AB Unavailable

L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2000 ACS
AN 1994:555414 CAPLUS
DN 121:155414
TI Interleukin 10 up-regulates elastin gene expression in vivo and in vitro at the transcriptional level
AU Reitamo, Sakari; Remitz, Anita; Tamai, Katsuto; Ledo, Isabel; Uitto, Jouni
CS Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, 19107, USA
SO Biochem. J. (1994), 302(2), 331-3
CODEN: BIJOAK; ISSN: 0264-6021
DT Journal
LA English
AB Recombinant human IL-10 at physiol. concns. had direct effects on the expression of the human elastin gene both in vivo and in vitro. Transgenic mice expressing a human elastin promoter/chloramphenicol acetyltransferase (CAT) reporter gene construct were injected s.c. with IL-10 (1-100 ng) and the site of injection was biopsied after 24 h. CAT assay revealed an increase of up to 3.5-fold in the promoter activity with 10 ng of IL-10. Transforming growth factor-.beta.2 (TGF-.beta.2) is known to up-regulate elastin gene expression in cultured fibroblasts. When IL-10 was added to such cultures, the effects of TGF-.beta.2 on elastin mRNA levels were synergistically potentiated. These results suggest that IL-10 has an up-regulatory effect on elastin gene expression.

=> d bib ab l7

L7 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
AN 95130069 MEDLINE
DN 95130069
TI Use of an intron polymorphism to localize the tropoelastin gene to mouse chromosome 5 in a region of linkage conservation with human chromosome 7.
AU Wydner K S; Sechler J L; Boyd C D; Passmore H C
CS Department of Biological Sciences, Rutgers University, Piscataway, New Jersey 08855-1059..
NC GM 46641 (NIGMS)
HL 39869 (NHLBI)
HL 42798 (NHLBI)
SO GENOMICS, (1994 Sep 1) 23 (1) 125-31.
Journal code: GEN. ISSN: 0888-7543.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U08210

EM 199504

AB The complete coding sequence for mouse tropoelastin was obtained from overlapping reverse transcriptase polymerase chain reaction (PCR) amplimers. These cDNA fragments were derived from mouse tropoelastin mRNA using PCR oligomers complementary to conserved domains within rat tropoelastin mRNA. A comparison of coding domains of mouse and rat tropoelastin mRNA revealed a greater than 93% homology at the nucleotide level and over 96% similarity in the predicted amino acid sequence. PCR primers complementary to regions of the mouse tropoelastin mRNA were used to define a novel intron length polymorphism (ILP) within intron 8 of the **mouse tropoelastin gene** (Eln). This ILP proved to be informative in an interspecific backcross in which genomic DNA samples from 75 backcross mice were used to map the tropoelastin gene to a position in the distal half of mouse chromosome 5. The linkage and genetic distances between Eln and the closest molecular markers used in this study are centromere-D5Mit95, D5Mit96-6.7 cM-Gus, Eln-4.0 cM-Zp3-telomere.

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interval between the echoes represents the fluid. Right heart catheterization and the injection of radiopaque contrast media to outline the cardiac chambers provides the most complete information and may be necessary to distinguish congestion due to heart disease from that due to pericardial effusion or scarring.

The mean pulmonary wedge pressure, the diastolic pressure in the pulmonary artery and right ventricle, and the mean right atrial pressure will be elevated and virtually identical if tamponade or restriction is present. The pulmonary arterial and right ventricular systolic pressures are only modestly elevated, so that pulse pressures are small. In the presence of tamponade, atrial pressure curves may show an accentuation of the Y descent, and ventricular pressure curves a diastolic dip at the time of rapid ventricular filling. These alterations in the pressure curves are always present if congestion results from restrictive pericarditis. While all of these hemodynamic abnormalities may also be found in severely congested states due to myocardial diseases, their presence combined with angiocardiographic evidence of a shadow surrounding the opacified cardiac chambers is sufficient to establish the diagnosis of pericardial fluid or thickening.

Treatment

General: For pain relief one may give, q. 4 h. if necessary, aspirin 0.6 Gm orally, codeine 15 to 60 mg orally, meperidine 50 to 100 mg orally or I.M., or morphine 10 to 15 mg subcut. Anxiety or insomnia may be alleviated by barbiturates (e.g., phenobarbital 15 to 30 mg orally t.i.d. or q.i.d. or pentobarbital 100 or 200 mg orally at bedtime).

Anticoagulants **should not be used** in pericardial disease. The exception is the transient pericarditis appearing within the first three days of an acute myocardial infarction, in which event anticoagulants should be given with caution and discontinued while a pericardial friction rub is audible.

Specific: Pericarditis due to bacterial or mycotic infections is treated with specific antimicrobial agents. Surgical drainage of the pericardial sac should be performed if pericarditis results from pyogenic infection. Antibiotics are not indicated in idiopathic pericarditis nor in the postinfarction or postpericardiotomy syndromes, but corticosteroids may be required to control pain, fever, and effusion. Prednisone 20 to 60 mg/day orally, in divided doses, may be given for 3 to 4 days. If the response is satisfactory, the dose is gradually reduced and may be discontinued in 7 to 14 days, though prolonged administration may be required. Therapy for pericarditis in rheumatic fever and the collagen diseases, and for pericardial involvement in neoplastic diseases, is directed at the underlying process. Surgical intervention is required in most instances of trauma to repair the injury and evacuate blood from the sac.

Immediate **pericardiocentesis** may be required when tamponade develops acutely; removal of even a small volume may be lifesaving. Premedication with morphine 8 to 15 mg or meperidine 50 to 100 mg, subcut., is desirable. The patient should be seated upright in a chair with his back supported. Under antiseptic conditions, the skin and subcut. tissues are infiltrated with 2% procaine HCl. A 3-in., short-beveled, 16-gauge needle is attached via a three-way stopcock to a 30 or 50 ml syringe. The pericardial sac may be entered (1) via the fifth left intercostal space 1 to 2 cm medial to the left border of cardiac flatness—the needle is directed inward and slightly medially; or (2) via the right or left xiphocostal angle or from the tip of the xiphoid process—the needle is directed inward, upward, and close to the chest wall. With constant suction applied to the syringe, the needle is advanced. The ECG should be monitored constantly, utilizing the aspirating needle as an exploring electrode by attaching it to the V lead of the electrocardiograph. If the needle touches the ventricular wall, ST segments become markedly elevated and ventricular premature contractions may appear. If repeated paracenteses are contemplated, a plastic catheter may be passed through the needle into the sac and the needle withdrawn.

Congestion due to the more gradual accumulation of fluid or to scarring may be alleviated to some extent by bed rest, salt restriction, and diuretics: meralluride 2 ml I.M. on alternate days for two or three doses or chlorothiazide 500 mg orally q.i.d. for two or three days. Digitalis is indicated if atrial arrhythmias or myocardial failure are present. Recurrent or persistent effusions, with or without tamponade, and restrictive pericarditis require pericardiectomy, preferably following institution of specific antimicrobial therapy.

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18. PRIMARY HYPERTENSION

(Benign Essential Hypertension)

A disorder of unknown origin characterized primarily by an elevated diastolic pressure associated with generalized arteriolar vasoconstriction.

Etiology

Heredity has been implicated as a predisposing factor, as well as ingestion of large amounts of sodium chloride. BP can be elevated in laboratory animals by renal, adrenal, and neurogenic mechanisms. The hypertension produced experimentally by constriction of the renal arteries (**Goldblatt hypertension**) closely resembles the human disease. Together with the renal involvement which is so common in the human disease, this strongly implicates

the kidneys in the pathogenesis as either an antecedent factor or as a consequence of primary hypertension. Renin, a protein of renal origin, has long been recognized as a hypertensive agent in man and animals, acting enzymatically on a circulating globulin to release the octapeptide, angiotensin, the most powerful pressor agent known. However, it is not known whether this system is overactive in human hypertension or even in the chronic phase of experimental renal hypertension. There is more convincing evidence that this humoral system is involved in the hypertension of unilateral renal disease and in malignant hypertension. Hypertensive disease can also be produced in laboratory animals by adrenal gluco- or mineralocorticoids—the counterpart of Cushing's syndrome and primary hyperaldosteronism in man. Moreover, adrenalectomy will ameliorate or prevent experimental Goldblatt hypertension. The source of renin is believed to be the juxtaglomerular cells of the kidney; aldosterone is made by the zona glomerulosa of the adrenal cortex. Since, via angiotensin generation, renin can cause increased aldosterone secretion, a renal-adrenal hormonal system for normal control of salt homeostasis has been proposed, and its derangement suggested as a factor in hypertension. Hypertension can also be produced in certain animals by interference with baroreceptors —buffer nerve hypertension. No human counterpart for this has been identified; however, considerable evidence suggests some role for the CNS in the pathogenesis of the human disease—e.g., the hyperresponsiveness of the vasculature to various stimuli, and the benefit afforded by tranquilizers, autonomic blocking agents, and sympathectomy.

Incidence

As many as 15% of adults in the USA are affected, women about twice as often as men. Obesity and diabetes mellitus are associated with hypertension. The accelerated (malignant) form of the disease develops in 1 to 5% of hypertensive individuals and is more common in men and in Negroes.

Pathology

Early in the disease there is no demonstrable pathologic change. The increased peripheral resistance is thought to be due to functional spasm. Later, widespread arteriolar sclerosis occurs with intimal hyalinization and medial hypertrophy. The lesions are prominent in the kidneys but are also found in the pancreas and liver.

Cardiac hypertrophy develops gradually. No multiplication of capillaries or demonstrable alteration in vascular tissue of the heart accompanies the cellular enlargement.

The frequent coincidence of coronary artery disease, CVAs, renal disease, and peripheral vascular changes makes it probable that primary hypertension accelerates the arteriosclerotic process in larger vessels as well.

The malignant form is characterized by widespread necrotizing arteriolitis with fibrinoid change and proliferative endarteritis, especially involving the kidneys.

Pathophysiology

In uncomplicated primary hypertension there is no change in cardiac output, blood volume or viscosity, pulse rate, or venous pressure. Except in the pulmonary circulation, which is normal, peripheral resistance is increased fairly uniformly throughout the body. Blood flow is unaffected because of the concomitant increase in arterial pressure.

In early stages, kidney function may be normal, but later a diminution in effective renal blood flow (and, to a lesser extent, impairment in maximal tubular excretory capacity) is observed. Impaired renal blood flow is the earliest demonstrable physiologic change. Indirect measurements suggest that muscle blood flow is increased. Thus, total flow (cardiac output) remains normal.

Lability of BP is characteristic initially. In many hypertensive subjects, BP returns to normal with rest, fever, or removal of emotional tensions, or following myocardial infarction or CVA.

Symptoms and Signs

Primary hypertension may be present for many years without other symptoms or signs. In the majority, increased BP first appears during the early 30's. Patients may complain of fatigue, nervousness, dizziness, palpitation, insomnia, weakness, and headaches. However, such complaints should not be attributed routinely to hypertension.

Cardiac hypertrophy is common, and ECG changes (left axis deviation, left ventricular strain, evidence of myocardial damage) may appear. Angina pectoris and myocardial infarction are frequent complications, while congestive failure occurs from coronary insufficiency and/or cardiac hypertrophy.

CVAs follow arteriosclerotic thrombosis or hemorrhage. Epistaxis and menorrhagia are not uncommon, but hemorrhage from other internal sites is rare.

Retinal abnormalities, secondary to sclerotic vascular changes, include arteriovenous compression, hemorrhages, exudates, or papilledema (*see* RETINOPATHIES *in* §13, Ch. 11). Acute recurrent attacks of severe headaches, vomiting, mental changes, and convulsions, associated with a rapidly rising BP, are infrequent manifestations of **"hypertensive encephalopathy"** and are probably due to cerebral vasoconstriction or edema.

Polyuria, nocturia, diminished ability of the kidney to concentrate, proteinuria, hematuria, cylindruria, and nitrogen retention eventually develop from arteriolar nephrosclerosis.

The accelerated form of hypertension should be suspected when

rapidly progressive renal damage, high diastolic pressure, and, often, retinopathy with papilledema occur.

Diagnosis

Hypertension is likely if the diastolic pressure rises even occasionally to > 95 mm Hg. The diagnosis becomes increasingly probable the more often this value is exceeded, and when emotional, physiologic, or arteriosclerotic factors can be excluded. Diagnosis of primary hypertension rests on the repeated finding of elevated diastolic pressure when other causes have been excluded.

Norepinephrine-producing pheochromocytomas (q.v. in §15, Ch. 4) may cause a curable hypertension clinically indistinguishable from primary hypertension. Tests with adrenolytics (e.g., phentolamine, piperoxan) will aid in the differentiation, as will determinations of urine or plasma catechols.

Other causes of hypertension include congenital and acquired primary disorders of the renal parenchyma or circulation, particularly acute and chronic glomerulonephritis, polycystic kidneys, pyelonephritis, and urinary tract obstruction; coarctation of the aorta; toxemias of pregnancy; primary aldosteronism; Cushing's syndrome; SLE; polyarteritis; acute intermittent porphyria; and some CNS disorders. Hyperthyroidism causes systolic hypertension only.

Prognosis

The course is extremely variable. The mean age at death for untreated patients is in the 50's, and their average life expectancy approaches 20 yr from onset, with wide extremes. Long survival is not a rarity. Untreated, the accelerated (malignant) form is usually fatal in < 2 yr.

The initial level or the maintained height of the casually recorded BP, or symptoms such as palpitation or headache, are not always correlated with the rate of progression or the development of complications. Conversely, a progressive hypertension, fixed high diastolic values, retinopathy, progressive renal damage, and coronary or arteriosclerotic vascular complications forecast a relatively short life expectancy.

Death results from congestive failure in about 50% of cases, from myocardial infarction and cerebral hemorrhage in about 20% each, and from uremia in about 10%.

Treatment

No known therapy can correct the abnormalities and reverse the course of the disease, but reduction of BP levels does appear to be beneficial.

General Measures: Restriction of normal activity is unnecessary in patients without symptoms or complications, but unusual physical or emotional stress should be avoided if possible. Overeating or intemperate drinking should also be avoided and obese patients should attempt to lose weight. Reduction of dietary sodium chloride to < 1 Gm/day significantly lowers the BP in about one-third of patients. However, it is extremely difficult for patients to adhere to the regimen and thiazide therapy has tended to make the low-salt diet obsolete.

Additional rest and mild sedatives (e.g., phenobarbital 30 mg b.i.d.) may help those with mild symptoms of uncomplicated hypertension. Headaches usually respond to aspirin 0.6 Gm orally; blocks placed under the head of the bed may be useful.

Congestive heart failure and other vascular complications should be treated in the usual manner. The therapy of arteriolar nephrosclerosis is the same as for chronic glomerulonephritis. Hypertension increases both the hazards of pregnancy and the fetal mortality rate. Prenatal supervision and induction of labor as soon as the fetus is viable are recommended. When the hypertension is clearly exacerbated, early termination of pregnancy may be necessary.

Specific Antihypertensive Therapy: Views on the value of specific antipressor therapy are changing. There is unanimous agreement that effective antihypertensive therapy can arrest the syndrome of malignant hypertension and prolong life. A lowering of BP may be followed by disappearance of papilledema, and by improved cardiac function with a reduction in heart size. Encephalopathic symptoms can be eliminated and renal function can improve, provided that renal perfusion is not compromised further by the lowered BP. However, it is possible that the accelerated or malignant form of hypertension is biochemically unique, in which case, the benefits of drug therapy in this form may not be applicable to less severe forms of hypertension. Recent evidence suggests that early therapy in the milder forms of the disease does have a beneficial effect upon life span and some physicians now treat patients with diastolic pressures < 100 mm Hg or even with labile hypertension. Since the question is not yet resolved, this discussion will be limited to the more conservative approach to therapy.

In deciding whether to treat a patient with primary hypertension, the physician must first observe the patient until the degree and pace of the disease process can be estimated. The advantages of drug therapy must then be weighed against its drawbacks, bearing in mind that often none of the available drugs are ideally effective and that they may cause annoying or even alarming side effects. In addition, it is not certain whether BP levels should be reduced to normal or whether partial reduction is equally beneficial. This is of practical importance since it is often difficult to reach and maintain normal BP levels without incurring unpleasant side effects. When vigorous antihypertensive therapy

is planned, the patient should be taught to measure his own BP.

A reasonable approach in deciding whether or not antihypertensive therapy is indicated is to classify patients based on the natural history of the disease. Accordingly, all patients with malignant hypertension should receive treatment. Patients with uncomplicated primary hypertension should be considered for therapy if the diastolic pressure is persistently > 110 mm Hg in males or > 115 in females, since females tolerate high BP better than males. All patients with evidence of vascular disease probably related to the hypertensive state are candidates for therapy. This includes those with (1) cerebral signs (encephalopathy), strokes, transient hemipareses, (2) cardiac insufficiency, coronary ischemia, ECG abnormalities—left ventricular hypertrophy or "strain," (3) evidence of progressive renal damage—increasing proteinuria or rising BUN, (4) Grade II retinopathy or more, and (5) severe headaches not controlled by other measures. However, patients with cerebral or coronary sclerosis or uremia may have reached a point where BP reduction is harmful rather than helpful.

A variety of antihypertensive drugs is available, which may be used alone or in combination, according to physician preference and patient response.

A thiazide diuretic (e.g., chlorothiazide 0.25 to 0.5 Gm b.i.d. or hydrochlorothiazide 25 to 50 mg b.i.d.) is the first approach. Potassium supplementation (potassium chloride 3 to 6 Gm/day, with due precautions) may be used, but often is unnecessary in ambulant patients with normal cardiorenal function. The antihypertensive action of thiazide diuretics seems to involve more than sodium depletion; they may also modify vascular tone.

Since thiazides appear to potentiate the effects of other antihypertensive agents, they are usually continued when the patient is treated with other agents. Reserpine 0.1 to 0.75 mg/day and related drugs can be used. Drowsiness, nasal stuffiness, gastric distress, bloating, and severe depression limit their use. They cause bradycardia and effectively block the tachycardia and headaches caused by hydralazine. Hydralazine 10 mg orally q.i.d. for two to four days, with gradual increases (depending on response) to as high as 1 Gm/day, may be effective. However, tolerance may develop, and the drug may produce psychoses, arthralgias, fever, rash, and, especially, a lupus-like syndrome which is not always reversible on stopping the drug. The drug increases cardiac output but whether this is helpful or harmful to hypertensive subjects is not clear. It should not be used in patients with known coronary artery disease.

Guanethidine 20 to 150 mg/day orally is a useful compound which interferes with the activity of the sympathetic nervous system. No serious toxicity has been reported, but unpleasant effects (e.g., exertional and postural hypotension, loss of ejaculation, morning weakness, diarrhea) may require reduction in dosage. Guanethidine **should not be used** with monoamine oxidase inhibitors (*see* §22, Ch. 13), and is **contraindicated** in patients with pheochromocytoma. Methyldopa is a synthetic amino acid which interferes with the activity or synthesis of endogenous norepinephrine. The dosage is 250 mg to 2 Gm/day orally in divided doses. It reduces the recumbent pressure and is relatively nontoxic. Drug fever and reversible hepatitis are rare toxic effects. Direct positive Coombs's tests have been observed, but seldom with associated hemolytic anemia.

Methyldopa and guanethidine have largely replaced the older ganglionic blocking agents. The oral dosages of the latter are: pentolinium 20 mg q. 8 h. with increases every 2 to 7 days, and mecamylamine 2.5 mg b.i.d. with increases at 2- to 4-day intervals. Pargyline is a monoamine oxidase inhibitor used as an antihypertensive agent. It also induces orthostatic hypotension. The drug increases brain catecholamine content and it may reverse depression induced by reserpine. It can also potentiate the action of a variety of CNS drugs, including alcohol. This drug, given orally in a dosage of 10 to 35 mg/day, should be reserved for severe hypertensive disease.

For **hypertensive crises (hypertensive encephalopathy)**, lumbar puncture or hypertonic solutions of magnesium sulfate, urea, or mannitol (1 L of 10% soln I.V. over 6 hr) may be of value. Parenteral reserpine (test dose, 0.25 mg I.M., then up to 2 mg/day or higher) may be effective, as may oral or I.V. methyldopa. In resistant patients, combined therapy including parenteral ganglionic blocking agents may be necessary. An experimental drug, diazoxide, given rapidly I.V. as a bolus (250 to 750 mg), can produce beneficial and sustained hypotensive effects, often without compromising renal function.

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19. AORTIC ARCH SYNDROME

(Pulseless Disease, Reversed Coarctation)

A clinical condition resulting from narrowing and occlusion of one or more of the large arterial vessels originating from the aortic arch and thoracic aorta and caused by inflammatory and/or atheromatous changes with secondary thrombosis.

The two prime causes of this uncommon syndrome are Takayasu's disease and Martorell's syndrome. Rare causes include syphilitic and tuberculous aortitis, aneurysms of the aortic arch, and aortic embolism. **Takayasu's disease** is of unknown etiology and occurs primarily in females aged 15 to 45, symptoms usually appearing when they are in their 20's. The innominate, carotid, and

orrhages and septal fibrosis are seen in the lungs. In the kidneys, focal glomerular capillary necrosis is followed by cellular proliferation and fibrosis. Patients usually present with hemoptysis, dyspnea, and microscopic hematuria and proteinuria. Gross hematuria is uncommon initially. Progressive azotemia (due to the nephritis) and anemia usually occur.

Prognosis and Treatment

Mortality rates are high. Corticosteroid therapy may benefit patients with predominantly pulmonary disease, and antilymphocytic serum may be useful. Bilateral nephrectomy and renal transplantation have resulted in prolonged survival and cessation of pulmonary hemorrhages in a few patients.

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26. COR PULMONALE

Enlargement of the right ventricle, with or without failure, secondary to disease of the lungs or pulmonary vasculature or to a disturbance in the respiratory act. The direct cause of the right ventricular enlargement is pulmonary arterial hypertension. Cor pulmonale (CP) is usually chronic but may be acute and reversible.

Etiology

The chronic obstructive lung diseases (chronic bronchitis and emphysema) are the most common causes of CP. Other causes include pulmonary granulomatoses (e.g., sarcoidosis, berylliosis); interstitial pulmonary fibrosis and conditions with "alveolar-capillary block," scleroderma, "primary" pulmonary hypertension, obesity with alveolar hypoventilation, massive loss of lung substance from surgery or trauma, kyphoscoliosis and other thoracic deformities, and neuromuscular disorders of the muscles of respiration. Acute CP is usually due to massive pulmonary embolization, but acute and reversible episodes of CP may also occur in patients with chronic lung disease if arterial hypoxia is acutely increased (e.g., during acute pulmonary infections).

Pathology

Pulmonary hypertension is caused by (1) an irreversible reduction in the vascular bed through disease affecting primarily the blood vessels (e.g., embolization, granulomatoses) or through massive loss of lung tissue, or by (2) arterial hypoxemia which causes pulmonary vasoconstriction. The chief causes of arterial hypoxemia are inadequate ventilation of perfused pulmonary alveoli, as seen in chronic bronchitis, emphysema, neurologic disorders, and chest

deformity; and impaired diffusion of O_2 across the pulmonary capillary membrane, as seen in pulmonary fibrosis. The respiratory acidosis associated with advanced chronic obstructive lung disease increases the hypertensive effect of arterial hypoxia.

The sequence of events with primary pulmonary vascular disease is straightforward. Initially, pulmonary hypertension appears only during episodes of increased pulmonary flow (e.g., fever or exercise). As the primary disease progresses, pulmonary hypertension becomes constant and leads to hypertrophy and dilation of the right ventricle, culminating in cardiac failure. Arterial hypoxemia may exacerbate the effect of pulmonary hypertension by inducing an increase in cardiac output and a secondary polycythemia with increased blood volume and viscosity, thus adding to the workload of the right ventricle.

Symptoms, Signs, and Diagnosis

CP should be suspected in all patients with the diseases mentioned above. In acute CP, signs of right heart dilation and failure appear early and are readily discernible. Initially, in chronic CP caused by disease of the lung parenchyma, the clinical manifestations of the primary disease overshadow those of CP. The major symptoms and signs (dyspnea, cough, asthma, cyanosis) are also seen in left heart failure and differentiation may be difficult. In chronic CP caused by pulmonary vascular disease, dyspnea may be slight or absent at rest, even with frank right ventricular failure. Some patients suffer syncopal attacks on exertion, and substernal pain, somewhat like angina, is not uncommon. Signs include a precordial systolic lift, a loud pulmonic second sound (P_2), and, if failure is present, distended jugular veins, hepatomegaly, and peripheral edema. In hypoxemic states, cyanosis, polycythemia, and clubbing of the fingers may be seen. Chest x-rays show enlargement of the right ventricle and the pulmonary artery. ECG evidence of right ventricular hypertrophy does not appear until late in the disease.

Treatment

Therapy of the primary pulmonary disorders is discussed under the appropriate chapter headings in this section on RESPIRATORY DISORDERS.

The therapy of right heart failure is discussed in §4, Ch. 12: CONGESTIVE HEART FAILURE.

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27. PULMONARY EDEMA

(*See* §4, Ch. 13)